Review Article

Personalized Medicine for the Management of Benign Prostatic Hyperplasia

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Abbreviations and Acronyms

5AR = 5α-reductase

5AR2 = 5α-reductase type 2

5ARI = 5α-reductase inhibitor

BPH = benign prostatic hyperplasia

DHT = dihydrotestosterone

GRP = gastrin releasing peptide

I-PSS = International Prostate Symptom Score

LUTS = lower urinary tract symptoms

PDE5-I = phosphodiesterase-5 inhibitor

SNP = single nucleotide polymorphism

TF = transcription factor

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Purpose: Benign prostatic hyperplasia affects more than 50% of men by age 60 years, and is the cause of millions of dollars in health care expenditure for the treatment of lower urinary tract symptoms and urinary obstruction. Despite the widespread use of medical therapy, there is no universal therapy that treats all men with symptomatic benign prostatic hyperplasia. At least 30% of patients do not respond to medical management and a subset require surgery. Significant advances have been made in understanding the natural history and development of the prostate, such as elucidating the role of the enzyme 5α-reductase type 2, and advances in genomics and biomarker discovery offer the potential for a more targeted approach to therapy. We review the current understanding of benign prostatic hyperplasia progression as well as the key genes and signaling pathways implicated in the process such as 5α-reductase. We also explore the potential of biomarker screening and gene specific therapies as tools to risk stratify patients with benign prostatic hyperplasia and identify those with symptomatic or medically resistant forms.

Materials and Methods: A PubMed® literature search of current and past peer reviewed literature on prostate development, lower urinary tract symptoms, benign prostatic hyperplasia pathogenesis, targeted therapy, biomarkers, epigenetics, 5α-reductase type 2 and personalized medicine was performed. An additional Google Scholar™ search was conducted to broaden the scope of the review. Relevant reviews and original research articles were examined, as were their cited references, and a synopsis of original data was generated with the goal of informing the practicing urologist of these advances and their implications.

Results: Benign prostatic hyperplasia is associated with a state of hyperplasia of the stromal and epithelial compartments, with 5α-reductase type 2 and androgen signaling having key roles in the development and maintenance of the prostate. Chronic inflammation, multiple growth factor and hormonal signaling pathways, and medical comorbidities have complex roles in prostate tissue homeostasis as well as its evolution into the clinical state of benign prostatic hyperplasia. Resistance to medical therapy with finasteride may occur through silencing of the 5α-reductase type 2 gene by DNA methylation, leading to a state in which 30% of adult prostates do not express 5α-reductase type 2. Novel biomarkers such as single nucleotide polymorphisms may be used to risk stratify patients with symptomatic benign prostatic hyperplasia and identify those at risk for progression or failure of medical therapy. Several inhibitors of the androgen receptor and other signaling pathways have recently been identified which appear to attenuate benign prostatic hyperplasia progression and may offer alternative targets for medical therapy.

Conclusions: Progressive worsening of lower urinary tract symptoms and bladder outlet obstruction secondary to benign prostatic hyperplasia is the result of multiple pathways including androgen receptor signaling, proinflammatory

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cytokines and growth factor signals. New techniques in genomics, proteomics and epigenetics have led to the discovery of aberrant signaling pathways, novel biomarkers, DNA methylation signatures and potential gene specific targets. As personalized medicine continues to develop, the ability to risk stratify patients with symptomatic benign prostatic hyperplasia, identify those at higher risk for progression, and seek alternative therapies for those in whom conventional options are likely to fail will become the standard of targeted therapy.

Key Words: prostate, prostatic hyperplasia, 5-alpha reductase inhibitors, finasteride, individualized medicine

Personalized medicine is an approach to medical care that tailors therapy to the individual characteristics of each patient. With advances in genomic analysis and the ability to develop biomarker assays and targeted therapeutics using small molecules, personalized medicine can more accurately diagnose disease, prognosticate those at risk for more aggressive disease and identify who will likely respond to a medication to help direct the optimal course of management, while minimizing morbidity and potential side effects from ineffective therapies. This approach can also improve efficiency and decrease the financial burden on the current health care system.

Lower urinary tract symptoms negatively impact quality of life for millions of patients and cost the United States health care system more than $4 billion each year.[1] These symptoms include voiding or obstructive symptoms such as weak stream, hesitancy and sensation of incomplete emptying, and storage or irritative symptoms such as urgency, frequency and nocturia. The etiology of LUTS includes urological, neurologic and comorbid conditions. While the hallmark of symptomatic BPH involves bladder outlet obstruction, other causes of LUTS include bladder cancer, prostate cancer, urinary tract infection, overactive bladder, urethral stricture, cerebrovascular accident or other neurologic injury, Parkinson disease, diabetes mellitus, congestive heart failure and obesity.[2] For personalized medicine to succeed in the treatment of LUTS, it should identify the specific disease which is the cause of the LUTS. In this review we focus on the application of personalized medicine for the management of bladder outlet obstruction secondary to BPH which, as previously mentioned, is one of the many causes of LUTS.

BPH appears to be associated with a state of hyperplasia of the stromal and epithelial compartments, with the enzyme 5AR2 having a key role in driving organ growth. The mainstays of medical therapy include 5α-reductase inhibitors and α-adrenergic blockers. However, at least 25% to 30% of patients do not respond to this therapy.[3] Understanding specific mechanisms and differential gene expression among individuals will allow for a better targeted approach to medical therapy. In this review we summarize the pathogenesis of BPH, and explore the current evidence about variably expressed genes and signaling pathways such as 5AR2. Recent advances in molecular biology and genomics offer the possibility of identifying and targeting specific pathways, and developing new strategies for BPH surveillance and treatment. We discuss the potential of biomarker screening and genetic based prescriptions as powerful tools to risk stratify patients with BPH and offer effective targeted therapy for symptomatic BPH.

PATHOGENESIS OF BPH

Since the first description of prostatic enlargement resulting in symptomatic bladder outlet obstruction in 1649,[4] much effort has been directed toward studying the development of the prostate gland. Understanding the pathophysiology of BPH can lead to the discovery of new biomarkers for personalized medicine. The prostate is the only male internal organ that continues to grow throughout adulthood and it grows at different rates in each individual (fig. 1).[5] Some have suggested that BPH may be caused by reactivation of a dormant embryonic growth process in the adult stroma.[6] Stromal-epithelial interactions, under the influence of the androgen receptor and dihydrotestosterone, are crucial to promote tissue expansion and form the hyperplastic benign nodules characteristic of the disease.[7]

Many cellular alterations including changes in proliferation, differentiation, quiescence and apoptosis have been implicated in the pathogenesis of BPH. Multiple families of growth factors act through paracrine signaling to stimulate proliferation, including fibroblast growth factor, epithelial growth factor, insulin-like growth factor, keratinocyte growth factor, hepatocyte growth factor and vascular endothelial growth factor.[8–10] DHT serves to modulate or augment these growth factor effects.

In addition to growth factor signaling, other proposed mechanisms for BPH progression include changes in androgen and estrogen levels with age,[11–13] loss of cell cycle regulators[8] and increased oxidative stress.[14] Chronic inflammation has been